IOSR Journal of Applied Chemistry (IOSRJAC)
ISSN : 2278-5736 Volume 1, Issue 4 (July-Aug. 2012), PP 20-23
www.iosrjournals.org

Synthesis of New 3, 5-Diaryl-4, 5-Dihydroisoxazole-4-Carbonitriles via 1, 3-Dipolar Cycloaddition Reaction

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Abstract: *Aromatic aldoximes **1a-i** undergo oxidative dehydrogenation with CrO_2 to give nitrile oxides, which are trapped in situ by 4-methoxycinnamonitrile **2** to afford of ethyl 3,5-diaryl-4,5-dihydroisoxazole-4-carbonitriles **3a-i** in good yield.*
***Key words**: Isoxazoles, isoxazolines, magtreive™, antimicrobial, antioxidant.*

I. Introduction

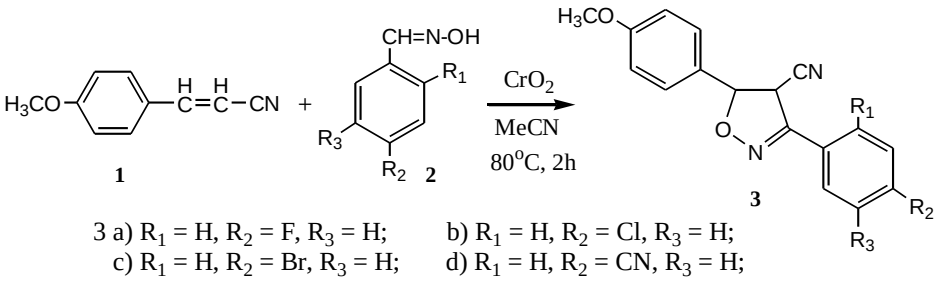
Isoxazoles and isoxazolines are very useful heterocycles in organic and heterocyclic chemistry [1]. Isoxazolines also serves as important building blocks for the synthesis of various biologically active molecules [2]. The isoxazoles are known to exhibit significant number of biological applications such as hypoglycemic, analgesic, anti-inflammatory and HIV-inhibitory activity [3], also found to exhibit antibacterial [4], antifungal [5], antioxidant [6], potent selective agonists at human cloned dopamine D4 receptors [7], COX-2 inhibitory [8], antinociceptive [9], anticancer [10], and antibiotic, antitumour, insecticidal activities [1,2]. They serve as prodrug for the anti-arithretic agent [11]. Vijay V. Dabholkar and co-workers [12] reported the synthesis and their antimicrobial activity of fused isoxazolines. Joshi and et al [13] reported that isoxazoles acts as potential antitubercular agents.

The most convenient synthesis of isoxazoline and isoxazole ring system has been executed in the literature via 1, 3-dipolar cycloaddition reactions of alkenes and alkynes with nitrile oxides generated *in situ* from aldoximes [2,14]. Rai et al developed new methods for generating nitrile oxides involving oxidative dehydrogenation of aldoximes using oxidants such as chloramine-T and mercuric acetate [15]. Treatment of aldoximes with Magtreive (CrO_2) in presence of dipolarophile furnished a variety of isoxazolines and isoxazoles as 1,3-dipoar cycloaddition products [16,17]. It was reported that nitrile oxides preferentially adds to olefinic C=C bond rather than C-N triple bond of acrylonitrile to form isoxazolines [18]. The classical method employed for the synthesis of isoxazolines involves 1,3-dipolar cycloaddition reactions of nitrile oxides to alkenes [19,20]. This paper describes the successful synthesis of new 3,5-diaryl-4,5-dihydroisoxazole-4-carbonitriles via 1.3-dipolar cycloaddition reactions

II. Materials And Methods

The chemicals/reagents used were purchased from sigma-aldrich chemicals (India) and Merck Chemicals (India). IR spectra were recorded on a Nujol mull on Shimadzu 8300 spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker supercon 400 MHz spectrophotometer using $CDCl_3$ as solvent and TMS as an internal standard. The Chemical shifts are expressed in δ ppm. Mass spectra were obtained on Shimadzu LCMS-2010A spectrophotometer (chemical ionization) and the important fragments are given with the relative intensities in the brackets. Elemental analysis was obtained on a Thermo Finnigan Flash EA 1112 CHN analyser. Thin layer chromatography (TLC) was performed on a pre-coated Silica Gel sheets (HF 254, sd-fine) using benzene: ethyl acetate (7:2) eluent and visualization of the spots was done in iodine vapour and UV light. Chromatographic separations were carried out on silica gel (70-230 mesh, Merck) column using hexane: ethyl acetate (8:1) as eluent.

In a general 1,3-dipolar cycloaddition reaction, a mixture of aromatic aldoximes **2,** 4-methoxy cinnamonitrile **1**, and CrO_2 in acetonitrile was stirred at 80^0C for 2 hours. The progress of the reaction was monitored by TLC. After the completion of the reaction and usual work up, the reaction mixture gave one major spot corresponding to the product 3,5-diaryl-4,5-dihydroisoxazole-4-carbonitrile **3** in TLC, and two minor spots corresponding to the un-reacted precursors. The products **3** were separated by column chromatography using hexane:ethyl acetate (8:1 v/v) and are obtained in 52-62% yield (Scheme-1).



3 a) R_1 = H, R_2 = F, R_3 = H; b) R_1 = H, R_2 = Cl, R_3 = H;
c) R_1 = H, R_2 = Br, R_3 = H; d) R_1 = H, R_2 = CN, R_3 = H;
e) R_1 = Cl, R_2 = H, R_3 = H; f) R_1 = NO_2, R_2 = H, R_3 = Cl;
g) R_1 = H, R_2 = OCH_3, R_3 = H; h) R_1 = H, R_2 = OCH_3, R_3 = OCH_3;
i) R_1 = H, R_2 = H, R_3 = H.

Scheme 1

III. Results And Discussion

The general synthetic pathway employed is depicted in the scheme-1. The structures of the cycloadducts were provided by IR, ^{1}H NMR, ^{13}C NMR, MS studies and elemental analysis. For instance, in IR spectra, the cycloadducts **3** gave the absorptions bands in the region 1650-1675 cm^{-1} for C=N (str) group which is a clear indication of the formation of cycloadducts, a strong and sharp absorption bands in the region 2220-2240 cm^{-1} for CN (str) which supports the fact that the C-N triple bond of CN group is unaffected during the cycloaddition reaction.

In ^{1}H NMR spectra, all substituted-4,5-dihydroisoxazole-4-carbonitriles **3** showed the peaks due to aromatic and substituent protons at the expected region. The consistent pattern signals due to C_4-H appear as doublet in the region δ 5.00-5.29 ppm., while signals due to C_5-H appears as doublet in the region δ 5.50-5.71 ppm. The coupling constant (*J*) values calculated for C_4-H and C_5-H were in range 7.0-9.6 *Hz*, these values suggests that both C_4-H and C_5-H are *cis* orientation and the cycloaddition took place in *cis* fashion. The appearance of these proton signals in the downfield was expected due to the strong electron withdrawing –CN group and aromatic ring bonded to C_4- and C_5- atoms respectively, which favors the formation of cycloadducts.
In ^{13}C NMR, all products gave the signals due to aromatic and substituent carbons at the expected region. The signals due to newly formed C_4-carbon appeared in the region δ_c 21.2-23.6 ppm, while, C_5-carbon showed the signals in the region δ_c 66.59-66.94 ppm and C_3-carbon showed the signals in the region δ_c 161.3-164.7 ppm. The signals due to CN group carbon appear in the region δ_c 116.2-118.0 ppm., which shows that the CN triple bond is unaffected during cycloaddition and is retained in the product. All substituted-4,5-dihydroisoxazole-4-carbonitriles **3** gave significantly stable molecular ion peaks with a relative abundance ranging from 08-46% and base peak at (MH^+). Further, all showed satisfactorily CHN analysis with a deviation of ±0.10% from the theoretically calculated values. All these observations strongly favor the formation of the cycloadducts.

IV. Experimental

4.1 Typical procedure for the preparation of *3-(4-fluorophenyl)-5-(4-methoxyphenyl)-4,5-dihydroisoxazole-4-carbonitrile* 3a: A mixture of 4-fluorobenzaldehyde oxime **2** (106mg, 0.76mmol, 1.2equiv), 3-(4-methoxyphenyl) acrylonitrile **1** (100mg, 0.63mmol, 1.0 equiv) were dissolved in 3 ml acetonitrile. Magtrieve^{TM} (530mg, 6.31 mmol, 10 equiv) was added and the reaction mixture was stirred under heating at 80^{0}C for 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through Celite bed. Magtrieve was washed with ethyl acetate (20 ml × 2). The combined filtrate was condensed to give the crude product, which was purified by column chromatography using hexane:ethyl acetate (8:1 v/v). The same procedure was used in all cases.

3a Obtained as light yellow oil in 62% yield. IR (Nujol): 1654 cm^{-1} C=N (str), 2228 cm^{-1} CN (str). ^{1}H NMR ($CDCl_3$): δ 3.84 (s, 3H, OCH_3), 5.29 (d, 1H, *J=7.2Hz*, C_4-H), 5.71 (d, 1H, *J=8.4Hz*, C_5-H), 6.90-6.93 (dd, 2H, Ar-H), 6.93-6.95 (dd, 2H, Ar-H), 7.38-7.40 (dd, 2H, Ar-H), 7.78-7.80 (dd, 2H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 21.2 (1C, 4-C), 55.1 (1C, OCH_3), 66.5 (1C, 5-C), 114.1-114.5 (2C, Ar-C), 115.6-115.9 (2C, Ar-C), 116.2 (1C, CN), 128.4-128.7 (2C, Ar-C), 129.2-129.5 (2C, Ar-C), 130.3 (1C, Ar-C), 130.6 (1C, Ar-C), 149.6 (1C, Ar-C), 161.3 (1C, 3-C), 161.7 (1C, Ar-C). MS (relative abundance) m/z: 297(MH^+, 100), 270 (32), 238 (20), 174 (16), 157 (44). Anal. Cacld. for $C_{17}H_{13}FN_2O_2$, C, 68.91, H, 4.42, N, 9.45%; Found: C, 68.85, H, 4.46, N, 9.37%.

4.2 Synthesis of *3-(4-Chlorophenyl)-5-(4-methoxyphenyl)-4,5-dihydroisoxazole-4-carbonitrile* 3b: Obtained from 4-methoxy cinnamonitrile **1** (100mg, 0.63mmol, 1.0equiv) and 4-chlorobenzaldehyde oxime **2** (118mg, 0.76mmol, 1.2equiv), as a light yellow oil in 54% yield. IR (Nujol): 1650 cm^{-1} C=N (str), 2220 cm^{-1} CN (str). ^{1}H NMR ($CDCl_3$): δ 3.84 (s, 3H, OCH_3), 5.28 (d, 1H, *J=9.0Hz*, C_4-H), 5.70 (d, 1H, *J=9.6Hz*, C_5-H), 6.91-6.92 (dd, 2H, Ar-H), 6.93-6.94 (dd, 2H, Ar-H), 7.38-7.40 (dd, 2H, Ar-H), 7.78-7.79 (dd, 2H, Ar-H). ^{13}C NMR ($CDCl_3$): δ

21.4 (1C, 4-C), 55.2 (1C, OCH$_3$), 66.8 (1C, 5-C), 114.2-114.4 (2C, Ar-C), 115.7-115.9 (2C, Ar-C), 116.6 (1C, CN), 128.5-128.7 (2C, Ar-C), 129.2-129.4 (2C, Ar-C), 130.7 (1C, Ar-C), 130.9 (1C, Ar-C), 150.2 (1C, Ar-C), 161.7 (1C, 3-C), 162.0 (1C, Ar-C). MS (relative abundance) m/z: 313 (MH^+, 100), 286 (28), 254 (24), 174 (18), 157 (42). Anal. Cacld. for $C_{17}H_{13}ClN_2O_2$, C, 65.29, H, 4.19, N, 8.96%; Found: C, 65.19, H, 4.18, N, 8.89%.

4.3 Synthesis of *3-(4-Bromophenyl)-5-(4-methoxyphenyl)-4,5-dihydroisoxazole-4-carbonitrile* 3c: Obtained from 4-methoxy cinnamonitrile **1** (100mg, 0.63mmol, 1.0equiv) and 4-bromobenzaldehyde oxime **2** (152mg, 0.76mmol, 1.2equiv), as a pale yellow oil in 52% yield. IR (Nujol): 1675 cm^{-1} C=N (str), 2240 cm^{-1} CN (str). ^{1}H NMR ($CDCl_3$): δ 3.86 (s, 3H, OCH_3), 5.19 (d, 1H, *J=7.6Hz*, C_4-H), 5.62 (d, 1H, *J=8.2Hz*, C_5-H), 6.91-6.93 (dd, 2H, Ar-H), 6.93-6.95 (dd, 2H, Ar-H), 7.38-7.41 (dd, 2H, Ar-H), 7.77-7.79 (dd, 2H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 22.3 (1C, 4-C), 55.6 (1C, OCH$_3$), 66.9 (1C, 5-C), 114.1-114.3 (2C, Ar-C), 116.8 (1C, CN), 125.1 (1C, Ar-C), 126.1-126.4 (2C, Ar-C), 128.5-128.7 (2C, Ar-C), 130.1-130.3 (2C, Ar-C), 131.9 (1C, Ar-C), 133.6 (1C, Ar-C), 152.5 (1C, Ar-C), 162.5 (1C, 3-C). MS (relative abundance) m/z: 357 (MH^+, ^{79}Br 100), 359 (MH^+, ^{79}Br 66), 332 (19), 330 (28), 300 (08), 298 (25), 174 (22), 157 (46). Anal. Cacld. for $C_{17}H_{13}BrN_2O_2$, C, 57.16, H, 3.67, N, 7.84%; Found: C, 57.10, H, 3.70, N, 7.78%.

4.4 Synthesis of *3-(4-Cyanophenyl)-5-(4-methoxyphenyl)-4,5-dihydroisoxazole-4-carbonitrile* 3d: Obtained from 4-methoxy cinnamonitrile **1** (100mg, 0.63mmol, 1.0equiv) and 4-cyanobenzaldehyde oxime **2** (111mg, 0.76mmol, 1.2equiv), as a colourless oil in 58% yield. IR (Nujol): 1658 cm^{-1} C=N (str), 2234 cm^{-1} CN (str). ^{1}H NMR ($CDCl_3$): δ 3.85 (s, 3H, OCH_3), 5.11 (d, 1H, *J=8.0Hz*, C_4-H), 5.54 (d, 1H, *J=8.2Hz*, C_5-H), 6.92-6.92 (dd, 2H, Ar-H), 7.22-7.24 (dd, 2H, Ar-H), 7.65-7.67 (dd, 2H, Ar-H), 7.98-7.99 (dd, 2H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 23.5 (1C, 4-C), 55.8 (1C, OCH$_3$), 66.9 (1C, 5-C), 114.4-114.6 (2C, Ar-C), 115.6 (1C, Ar-C), 116.9 (1C, CN), 118.0 (1C, CN), 126.8-126.9 (2C, Ar-C), 129.0-129.1 (2C, Ar-C), 131.0-131.2 (2C, Ar-C), 132.3 (1C, Ar-C), 136.7 (1C, Ar-C), 159.7 (1C, Ar-C), 163.2 (1C, 3-C). MS (relative abundance) m/z: 304 (MH^+, 100), 277 (21), 245 (30), 174 (23), 157 (41). Anal. Cacld. for $C_{18}H_{13}N_3O_2$, C, 71.28, H, 4.32, N, 13.85%; Found: C, 71.21, H, 4.24, N, 13.79%.

4.5 Synthesis of *3-(2-Chlorophenyl)-5-(4-methoxyphenyl)-4,5-dihydroisoxazole-4-carbonitrile* 3e: Obtained from 4-methoxy cinnamonitrile **1** (100mg, 0.63mmol, 1.0equiv) and 2-chlorobenzaldehyde oxime **2** (118mg, 0.76mmol, 1.2equiv), as a colorless oil in 55% yield. IR (Nujol): 1668 cm^{-1} C=N (str), 2235 cm^{-1} CN (str). ^{1}H NMR ($CDCl_3$): δ 3.87 (s, 3H, OCH_3), 5.00 (d, 1H, *J=8.4Hz*, C_4-H), 5.50 (d, 1H, *J=8.6Hz*, C_5-H), 6.91-6.93 (dd, 2H, Ar-H), 7.23-7.24 (dd, 2H, Ar-H), 7.39-7.41 (dd, 2H, Ar-H), 7.669-7.681 (dd, 2H, Ar-H). Anal. Cacld. for $C_{17}H_{13}ClN_2O_2$, C, 65.29, H, 4.19, N, 8.96%; Found: C, 65.22, H, 4.22, N, 8.89%.

4.6 Synthesis of *3-(5-Chloro-2-nitrophenyl)-5-(4-methoxyphenyl)-4,5-dihydroisoxazole-4-carbonitrile* 3f: Obtained from 4-methoxy cinnamonitrile **1** (100mg, 0.63mmol, 1.0equiv) and 5-chloro-2-nitrobenzaldehyde oxime **2** (152mg, 0.76mmol, 1.2equiv), as a light yellow oil in 53% yield. IR (Nujol): 1668 cm^{-1} C=N (str), 2230 cm^{-1} CN (str). ^{1}H NMR ($CDCl_3$): δ 3.79 (s, 3H, OCH_3), 5.12 (d, 1H, *J=8.1Hz*, C_4-H), 5.51 (d, 1H, *J=9.0Hz*, C_5-H), 6.92-6.93 (dd, 2H, Ar-H), 7.23-7.24 (dd, 2H, Ar-H), 7.70 (dd, 1H, Ar-H), 8.11 (d, 1H, Ar-H), 8.20 (dd, 1H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 23.6 (1C, 4-C), 55.8 (1C, OCH$_3$), 66.8 (1C, 5-C), 114.3-114.5 (2C, Ar-C), 116.7 (1C, CN), 124.1 (1C, Ar-C), 127.0-127.2 (2C, Ar-C), 130.3 (1C, Ar-C), 131.2 (1C, Ar-C), 132.8 (1C, Ar-C), 132.9 (1C, Ar-C), 136.1 (1C, Ar-C), 140.1 (1C, Ar-C), 159.9 (1C, Ar-C), 164.2 (1C, 3-C). MS (relative abundance) m/z: 358 (MH^+, ^{35}Cl, 100), 360 (MH^+, ^{37}Cl, 33), 333 (08), 331 (22), 299 (34), 174 (22), 157 (40). Anal. Cacld. for $C_{17}H_{12}ClN_3O_4$, C, 57.07, H, 3.38, N, 11.75%; Found: C, 57.00, H, 3.43, N, 11.78%.

4.7 Synthesis of *3,5-Bis(4-methoxyphenyl)-4,5-dihydroisoxazole-4-carbonitrile* 3g: Obtained from 4-methoxy cinnamonitrile **1** (100mg, 0.63mmol, 1.0equiv) and 4-methoxybenzaldehyde oxime **2** (115mg, 0.76mmol, 1.2equiv), as a colourless oil in 60% yield. IR (Nujol): 1655 cm^{-1} C=N (str), 2225 cm^{-1} CN (str). ^{1}H NMR ($CDCl_3$): δ 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 5.13 (d, 1H, *J=8.1Hz*, C_4-H), 5.51 (d, 1H, *J=8.8Hz*, C_5-H), 6.92-6.93 (dd, 2H, Ar-H), 6.99-6.70 (dd, 2H, Ar-H), 7.22-7.23 (dd, 2H, Ar-H), 7.74-7.75 (dd, 2H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 23.5 (1C, 4-C), 55.7 (1C, OCH$_3$), 55.8 (1C, OCH$_3$), 66.8 (1C, 5-C), 114.3-114.4 (2C, Ar-C), 116.6 (1C, CN), 124.2 (1C, Ar-C), 127.1-127.2 (2C, Ar-C), 130.2 (1C, Ar-C), 131.2 (1C, Ar-C), 132.9 (1C, Ar-C), 133.0 (1C, Ar-C), 136.0 (1C, Ar-C), 140.1 (1C, Ar-C), 159.9 (1C, Ar-C), 164.2 (1C, 3-C). MS (relative abundance) m/z: 309 (MH^+, 100), 282 (36), 250 (32), 174 (27), 157 (42). Anal. Cacld. for $C_{18}H_{16}N_2O_3$, C, 70.12, H, 5.23, N, 9.09%; Found: C, 70.06, H, 5.26, N, 9.10%.

4.8 Synthesis of *3-(3,4-Dimethoxyphenyl)-5-(4-methoxyphenyl)-4,5-dihydroisoxazole-4-carbonitrile* 3h: Obtained from 4-methoxy cinnamonitrile **1** (100mg, 0.63mmol, 1.0equiv) and 3,4-dimethoxybenzaldehyde oxime **2** (138mg, 0.76mmol, 1.2equiv), as a colourless oil in 61% yield. IR (Nujol): 1672 cm^{-1} C=N (str), 2238 cm^{-1} CN (str). ^{1}H NMR ($CDCl_3$): δ 3.81 (s, 6H, OCH_3), 3.81 (s, 3H, OCH_3), 5.12 (d, 1H, *J=8.5Hz*, C_4-H), 5.52 (d, 1H, *J=9.2Hz*, C_5-H), 6.92-6.93 (dd, 2H, Ar-H), 6.99 (dd, 1H, Ar-H), 7.23-7.24 (dd, 2H, Ar-H), 7.30 (s, 1H, Ar-H), 7.40 (dd, 1H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 23.4 (1C, 4-C), 55.8 (1C, OCH$_3$), 55.8 (1C, OCH$_3$), 55.8 (1C,

O<u>C</u>H$_3$), 66.8 (1C, 5-<u>C</u>), 112.1 (1C, Ar-<u>C</u>), 114.2-114.3 (3C, Ar-<u>C</u>), 116.6 (1C, <u>C</u>N), 121.2 (1C, Ar-<u>C</u>), 127.1-127.3 (3C, Ar-<u>C</u>), 148.7 (1C, Ar-<u>C</u>), 149.1 (1C, Ar-<u>C</u>), 150.4 (1C, Ar-<u>C</u>), 158.9 (1C, Ar-<u>C</u>), 164.2 (1C, 3-<u>C</u>). MS (relative abundance) m/z: 339 (MH^+, 100), 312 (19), 280 (33), 174 (26), 157 (45). Anal. Cacld. for $C_{19}H_{18}N_2O_4$, C, 67.44, H, 5.36, N, 8.28%; Found: C, 67.38, H, 5.32, N, 8.21%.

4.9 Synthesis of *5-(4-Methoxyphenyl)-3-phenyl-4,5-dihydroisoxazole-4-carbonitrile* 3i: Obtained from 4-methoxy cinnamonitrile **1** (100mg, 0.63mmol, 1.0equiv) and benzaldehyde oxime **2** (92mg, 0.76mmol, 1.2equiv), as a colourless oil in 56% yield. IR (Nujol): 1670 cm^{-1} C=N (str), 2235 cm^{-1} CN (str). ^{1}H NMR ($CDCl_3$): δ 3.82 (s, 3H, OCH_3), 5.13 (d, 1H, *J=9.0Hz*, C_4-H), 5.53 (d, 1H, *J=8.5Hz*, C_5-H), 6.91-6.93 (dd, 2H, Ar-H), 7.20-7.22 (dd, 2H, Ar-H), 7.56-7.78 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 23.4 (1C, 4-<u>C</u>), 55.8 (1C, O<u>C</u>H$_3$), 66.7 (1C, 5-<u>C</u>), 114.3 (2C, Ar-<u>C</u>), 116.6 (1C, <u>C</u>N), 127.0 (2C, Ar-<u>C</u>), 128.2 (2C, Ar-<u>C</u>), 128.4 (2C, Ar-<u>C</u>), 131.1 (1C, Ar-<u>C</u>), 133.0 (1C, Ar-<u>C</u>), 133.6 (1C, Ar-<u>C</u>), 159.0 (1C, Ar-<u>C</u>), 164.7 (1C, 3-<u>C</u>). MS (relative abundance) m/z: 279 (MH^+, 100), 252 (22), 220 (30), 174 (20), 157 (38). Anal. Cacld. for $C_{17}H_{14}N_2O_2$, C, 73.37, H, 5.07, N, 10.07%; Found: C, 73.30, H, 5.01, N, 10.02%.

V. Conclusion

The successful synthesis of new compounds with the use of CrO_2 as catalytic dehydrogenating agents validates the significance of this study. However, the modification in the procedure for improving the yield of the products remains of interest.

VI. Acknowledgements

One of the authors (PJR) is grateful to the University Grants Commission, New Delhi, for the award of Teacher Fellowship and Financial Support.

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